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ORIGINAL REPORT

Treatment of Stage IV Favorable Histology Wilms Tumor With Lung Metastases: A Report From the Children's Oncology Group AREN0533 Study

David B. Dix, Nita L. Seibel, Yueh-Yun Chi, Geetika Khanna, Eric Gratias, James R. Anderson, Elizabeth A. Mullen, James I. Geller, John A. Kalapurakal, Arnold C. Paulino, Elizabeth J. Perlman, Peter F. Ehrlich, Marcio Malogolowkin, Julie M. Gastier-Foster, Elizabeth Wagner, Paul E. Grundy, Conrad V. Fernandez, and Jeffrey S. Dome

Author affiliations and support information (if applicable) appear at the end of this article.

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Corresponding author: Jeffrey S. Dome, MD, PhD, Center for Cancer and Blood Disorders, Children's National Health System, 111 Michigan Ave NW, Washington, DC 20010; e-mail: jdome@childrensnational.org.

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ABSTRACT

Purpose

The National Wilms Tumor Study (NWTS) treatment of favorable histology Wilms tumor with lung metastases was vincristine/dactinomycin/doxorubicin (DD4A) and lung radiation therapy (RT). The AREN0533 study applied a new risk stratification and treatment strategy to improve event-free survival (EFS) while reducing exposure to lung RT.

Methods

Patients with favorable histology Wilms tumor and isolated lung metastases showing complete lung nodule response (CR) after 6 weeks of DD4A continued receiving chemotherapy without lung RT. Patients with incomplete response (IR) or loss of heterozygosity at chromosomes 1p/16q received lung RT and four cycles of cyclophosphamide/etoposide in addition to DD4A drugs (Regimen M). AREN0533 was designed to preserve a 4-year EFS of 85% for lung nodule CR and improve 4-year EFS from 75% to 85% for lung nodule IR.

Results

Among 292 assessable patients, 133 had CR and 159 had IR. For patients with CR, 4-year EFS and overall survival (OS) estimates were 79.5% (95% CI, 71.2% to 87.8%) and 96.1% (95% CI, 92.1% to 100%), respectively. Expected versus observed event rates were 15% and 20.2% ($P = .052$), respectively. For patients with IR, 4-year EFS and OS estimates were 88.5% (95% CI, 81.8% to 95.3%) and 95.4% (95% CI, 90.9% to 99.8%), respectively. Expected versus observed event rates were 25% and 12.2% ($P < .001$), respectively. Overall, 4-year EFS and OS were 85.4% (95% CI, 80.5% to 90.2%) and 95.6% (95% CI, 92.8% to 98.4%) compared with 72.5% (95% CI, 66.9% to 78.1%; $P < .001$) and 84.0% (95% CI, 79.4% to 88.6%; $P < .001$), respectively, in the predecessor NWTS-5 study.

Conclusion

Excellent OS was achieved after omission of primary lung RT in patients with lung nodule CR, although there were more events than expected. EFS was significantly improved, with excellent OS, in patients with lung nodule IR using four cycles of cyclophosphamide/etoposide in addition to DD4A drugs. The overall AREN0533 treatment strategy yielded EFS and OS estimates that were superior to previous studies.

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INTRODUCTION

Patients with stage IV favorable histology Wilms tumor (FHWT), the majority of whom have pulmonary metastases, have inferior outcomes compared with those with localized disease.[1,2] Their treatment is also complicated by a risk of late effects, including cardiac dysfunction, lung toxicity, musculoskeletal and soft tissue defects, and second malignancies.[3,4]

Two distinct treatment approaches for patients with FHWT and lung metastases have been used. In the approach adopted by the International Society of Pediatric Oncology (SIOP), patients were treated with 6 weeks of vincristine/dactinomycin/doxorubicin chemotherapy before nephrectomy. If lung nodule complete response (CR) was

ASSOCIATED CONTENT

Appendix
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attained by either chemotherapy or surgical resection, patients did not receive lung radiation therapy (RT). The cumulative anthracycline dosage in the most recently reported trial (SIOP 93-01) was 350 mg/m^2, and the 5-year event-free survival (EFS) and overall survival (OS) estimates among patients with nonanaplastic Wilms tumor and lung metastasis were 77% and 87%, respectively.[5] A subgroup of the SIOP 93-01 and SIOP-2001 populations analyzed by the German Society of Pediatric Oncology/Hematology that included all histologic subtypes indicated that lung nodule response after 6 weeks of chemotherapy had prognostic significance: 5-year EFS estimates were 17% for patients with radiographically stable or progressive lung nodules, 67% for patients achieving partial response (PR), and 79% for patients achieving CR after 6 weeks of chemotherapy.[6] In the approach used by the National Wilms Tumor Studies (NWTS), all patients with lung metastasis received lung RT, regardless of lung nodule response. In NWTS-5, the cumulative doxorubicin dosage was 150 mg/m^2, and the 5-year EFS for patients with FHWT and isolated lung metastases was 76%.[7] The inferior outcome for patients with incomplete lung nodule response (IR) seen in the German Society of Pediatric Oncology/Hematology study was affirmed in an unpublished retrospective analysis of NWTS-5, which showed 5-year EFS of 85% for patients with lung nodule CR versus 74% for those without CR by day 70. In addition, NWTS-5 showed that tumor-specific loss of heterozygosity (LOH) of chromosomes 1p and 16q was associated with an adverse prognosis, with 4-year EFS and OS estimates of 65.9% and 77.7%, respectively, in patients with stage III and IV disease with combined LOH at 1p/16q.[2]

The AREN0533 study (Treatment of Newly Diagnosed Higher-Risk Favorable Histology Wilms Tumor) applied a new strategy for patients with FHWT and isolated lung metastases to improve EFS while reducing exposure to lung RT. Therapy was adjusted based on lung nodule response and tumor-specific LOH at 1p and 16q. We describe the results of this strategy and a post hoc analysis of the prognostic significance of 1q gain, which has been shown to be a powerful prognostic factor for FHWT.[8-10]

METHODS

Patients

Patients were enrolled in the AREN03B2 Renal Tumor Biology and Classification Study, where real-time central review of surgical reports, pathology slides, and computed tomography (CT) scans was performed to confirm eligibility for AREN0533. Institutional review board approval was obtained before enrollment. Authorization for participation was obtained from parents or legal guardians, as well as age-appropriate assent. This study was monitored by an independent Data Safety Monitoring Board.

Lung nodules were considered as metastatic disease if they were round, noncalcified, and not in a pulmonary fissure. All patients with isolated lung nodules underwent repeat chest CT scans, which were centrally reviewed, after 6 weeks of chemotherapy. Testing of tumor-specific LOH at chromosomes 1p and 16q was conducted by the Children's Oncology Group (COG) Biopathology Center as previously described or by capillary electrophoresis of fluorescently detected short tandem repeat markers.[2] Testing for chromosome 1q gain was performed by multiplex ligation-dependent probe amplification as previously described.[10]

Treatment

Surgery. Radical nephrectomy with lymph node sampling was recommended according to previously reported guidelines; a minimum of a needle biopsy was required for unresectable tumors.[11] Biopsy or resection of lung nodules of unclear significance was recommended at initial diagnosis and/or after the first 6 weeks of chemotherapy. If all lung nodules were proven not to have viable malignant cells, the patient did not receive lung RT. Patients who achieved CR by pulmonary metastasectomy with viable tumor were treated with four cycles of cyclophosphamide/etoposide in addition to vincristine/dactinomycin/doxorubicin (DD4A) drugs (Regimen M) and lung RT.

Chemotherapy. Patients were treated with DD4A for the first 6 weeks of therapy (Fig 1). Additional therapy was stratified based on lung nodule response at week 6. Patients showing CR continued receiving DD4A without lung RT. Patients with PR or stable disease (SD), or with combined LOH at 1p and 16q, were treated with Regimen M and lung RT.

Radiation therapy. For local stage III tumors, flank/abdominal RT was delivered by week 2 for patients who underwent nephrectomy at diagnosis and by week 7 for patients who received preoperative chemotherapy. For patients requiring lung RT, therapy was delivered at week 7 after assessment of response. When lung and abdominal fields were treated during separate sessions, the fields overlapped inferiorly to avoid underdosage at the match line (Fig 1).

Statistical Analysis

For patients with pulmonary CR at week 6, the study was designed to preserve at least 85% 4-year EFS when treated with DD4A without lung RT. The study provided 90% power (testing at the 10% level of statistical significance [one-sided]) to detect an increase in the risk of events for these patients to 1.694 (corresponding to a 4-year EFS of approximately 76%). For patients with lung nodule IR at week 6, the study was designed to

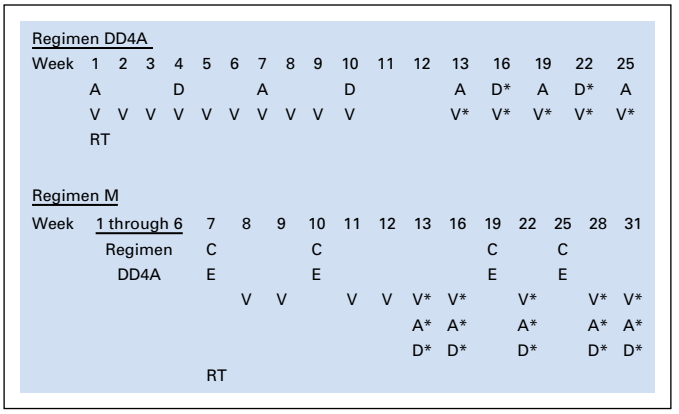

Fig 1. Treatment regimens used in AREN0533. V: vincristine: 0.025 mg/kg/dose intravenously (IV) × 1 for infants < 1 year; 0.05 mg/kg/dose IV × 1 for children ≥ 1 year to 2.99 years; 1.5 mg/m^2/dose IV × 1 for children ≥ 3 years (maximum dose: 2 mg). V(*): vincristine: 0.034 mg/kg/dose IV × 1 for infants < 1 year; 0.067 mg/kg/dose IV × 1 for children ≥ 1 year to 2.99 years; 2 mg/m^2/dose IV × 1 for children ≥ 3 years (maximum dose: 2 mg). A: dactinomycin 0.023 mg/kg/dose IV × 1 for infants < 1 year; 0.045 mg/kg/dose IV × 1 for children ≥ 1 year (maximum dose: 2.3 mg). D: doxorubicin 1.5 mg/kg/dose IV × 1 for infants < 1 year; 45 mg/m^2/dose IV × 1 for children ≥ 1 year. D(*): doxorubicin 1 mg/kg/dose IV × 1 for infants < 1 year; 30 mg/m^2/dose IV × 1 for children ≥ 1 year. C: cyclophosphamide 14.7 mg/kg/dose IV × 5 days for infants < 1 year; 440 mg/m^2/dose IV × 5 days for children ≥ 1 year. E: etoposide 3.3 mg/kg/dose IV × 5 days for infants < 1 year; 100 mg/m^2/dose IV × 5 days for children ≥ 1 year. Radiation therapy (RT): for local stage III tumors, 10.8 Gy flank radiation was used, with a 10.8 Gy boost for gross residual disease after surgery. Patients with preoperative tumor rupture, cytology-positive ascites, or diffuse peritoneal seeding were treated with whole-abdomen RT to a dose of 10.5 Gy. Patients with incomplete lung nodule response received whole-lung RT to a dose of 12 Gy in 1.5 Gy fractions (reduced to 10.5 Gy for patients < 12 months). DD4A, vincristine/dactinomycin/doxorubicin; M, four cycles of cyclophosphamide/etoposide in addition to DD4A drugs.

improve 4-year EFS from 75% to 85% with Regimen M. The study provided 90% power (testing at the 10% level of statistical significance [one-sided]) to detect a decrease in the risk of events for these patients when treated with regimen M to 0.587 (corresponding to a 4-year EFS of approximately 84%). Events were defined as relapse, second malignancy, or death. Both EFS and OS were calculated based on the Kaplan-Meier method. The 95% CIs were computed using the Peto-Peto estimate of the SE. The log-rank test was used to make comparisons with historical standards. Statistical significance was considered at the .05 level. Statistical analyses were completed using SAS 9.4 (SAS Institute, Cary, NC). The June 30, 2016, data freeze was used.

RESULTS

AREN0533 was activated on February 26, 2007, and closed to accrual on May 24, 2013. Two hundred ninety-seven patients with isolated pulmonary nodules were found to be eligible after central review. The patient demographics are listed in Table A1, and treatment assignments are described in Figure 2. Fifty-two patients with extrapulmonary metastases, with or without lung nodules, will be described separately.

One hundred eighty-eight patients underwent immediate nephrectomy, and 109 received preoperative chemotherapy. The local stage distribution was stage I (n = 10), II (n = 50), and III (n = 237). One hundred seventeen patients had radiologic pulmonary CR, and 175 had IR (five had incomplete data). Among the patients with IR, 12 had SD and the remainder showed PR.

Eight of the 12 patients with SD underwent lung nodule biopsy; seven did not show evidence of malignancy (one with pulmonary fibrosis, one with diffuse alveolar histiocytes, and five not further specified). In one, the nodule was missed by biopsy. An additional 15 patients with PR underwent biopsy; nine showed no evidence of tumor (one with fibrosis, one with chronic bronchiolitis, two with inflammatory changes, one with intrapulmonary lymph node, one with subpleural calcification, and three not specified). Six had tumor, of whom five received Regimen M and lung RT and one received DD4A with lung RT because of parent choice. In total, 16 patients with radiologic lung nodule IR were classified as having CR on the basis of the biopsy results and were treated accordingly, bringing the number of patients with CR to 133 (Fig 2).

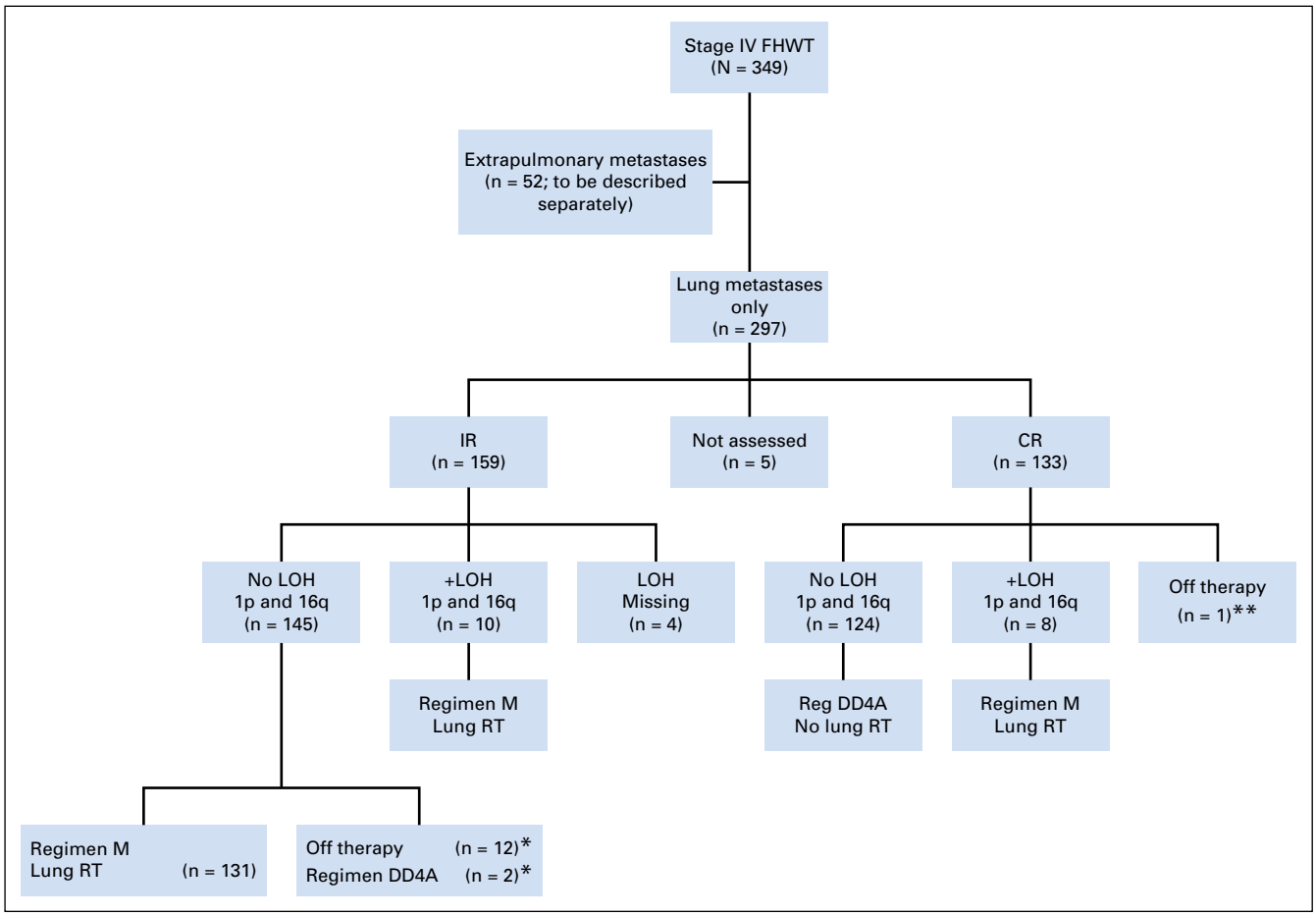

Fig 2. CONSORT diagram of patients with pulmonary nodules without other metastatic sites included in the AREN0533 study. (*) Twelve patients with lung nodule incomplete response (IR) came off therapy before starting lung radiation therapy (RT) and four cycles of cyclophosphamide/etoposide in addition to vincristine/dactinomycin/doxorubicin (DD4A) drugs (Regimen M) for the following reasons: patient was subsequently found to have anaplasia on delayed nephrectomy (n = 1), physician determined it was in the patient's best interest (n = 4), progressive disease (n = 2), or refusal of additional protocol therapy by patient/parent/guardian (n = 7). An additional two patients received DD4A therapy against protocol guidelines. (**) One patient with lung nodule complete response (CR) came off therapy because the physician thought it was in the patient's best interest. FHWT, favorable histology Wilms tumor; LOH, loss of heterozygosity.

The proportion of patients achieving CR at week 6 correlated with the initial maximum lung nodule size: 33 of 150 (22.0%) for > 10 mm; 39 of 66 (59.0%) for 6 to 10 mm; 36 of 52 (69.2%) for 3 to 5 mm, and 25 of 29 (86.2%) for 1 to 2 mm. Likewise, the proportion of patients achieving CR correlated with the total number of lung nodules visible on CT scans: 18 of 102 (17.6%) for more than 10; 22 of 52 (42.3%) for 6 to 10; 50 of 84 (59.5%) for 2 to 5; and 43 of 59 (72.9%) for a solitary nodule.

Outcomes

The median follow-up time was 4.72 years. Of 124 patients without LOH and with lung nodule CR who received DD4A without RT (Fig 2), the 4-year EFS and OS were 79.5% (95% CI, 71.2% to 87.8%) and 96.1% (95% CI, 92.1% to 100%), respectively (Fig 3). Under the null hypothesis EFS of 85%, the expected and observed event rates were 15% (18 of 120) and 20.2% (25 of 124; one-sided $P = .052$). Twenty-four patients experienced relapse, and one had a second malignancy (acute myelogenous leukemia). The median time from enrollment to first relapse was 0.81 years (range, 0.38 to 3.11 years). The sites of relapse were lung only (n = 22), liver and lung (n = 1), and abdomen (n = 1).

Of 131 patients without LOH who had IR and received Regimen M and lung RT, the 4-year EFS and OS estimates were 88.5% (95% CI, 81.8% to 95.3%) and 95.4% (95% CI, 90.9% to 99.8%; Fig 4). Under the null hypothesis EFS of 75%, the expected and observed event rates were 25% (30 of 120) and 12.2% (16 of 131; one-sided $P < .001$). Fourteen patients experienced relapse, one had a second malignancy (parotid mucoepidermoid carcinoma), and one died from an unknown cause. The median time to first relapse was 0.88 years (range, 0.70 to 1.50 years). The sites of relapse were lung only (n = 9), abdomen and tumor bed (n = 3), lung and abdomen (n = 1), and brain (n = 1). The 4-year EFS and OS according to local stage were stage I, 80% (95% CI, 51.4% to 100%) and 100%; stage II, 90% (95% CI, 80.0% to 100%) and 94% (95% CI, 85.7% to 100%); and stage III, 85% (95% CI, 79.0% to 90.2%) and 95.8% (95% CI, 92.7% to 98.9%), respectively.

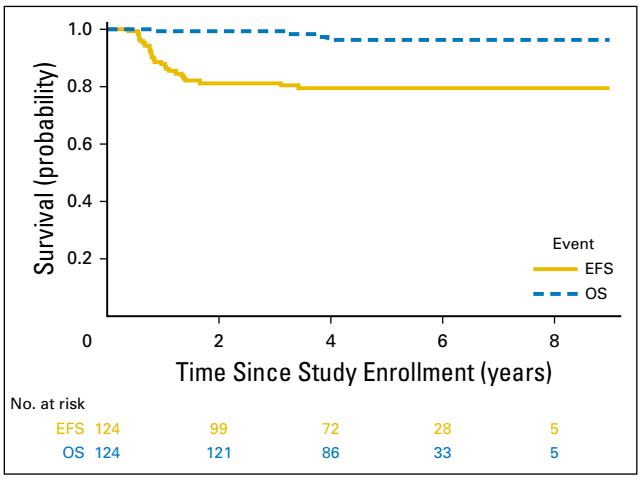

Fig 3. Event-free survival (EFS) and overall survival (OS) for patients with lung nodule complete response who completed treatment with vincristine/dactinomycin/doxorubicin without lung radiation therapy.

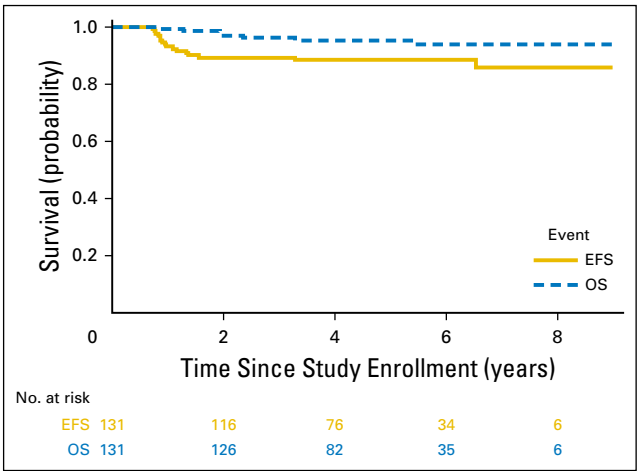

Fig 4. Event-free survival (EFS) and overall survival (OS) for patients with incomplete lung nodule response without loss of heterozygosity who completed treatment with lung radiation therapy and four cycles of cyclophosphamide/etoposide in addition to vincristine/dactinomycin/doxorubicin.

Effect of LOH 1p/16q and Chromosome 1q Gain

Of 18 patients with pulmonary metastases only and LOH at 1p and 16q, eight had lung nodule CR and 10 had IR. All of these patients received Regimen M and lung RT, with 4-year EFS and OS estimates of 100%. We conducted a post hoc analysis of the prognostic significance of tumor 1q gain in 212 patients enrolled in AREN0533 with isolated pulmonary metastases and available tumor DNA (Table 1). For patients with lung nodule CR, 4-year EFS was significantly worse for patients with 1q gain, with a trend toward inferior OS. Relapses in patients with CR and 1q gain were predominantly pulmonary (nine of 11). For patients with incomplete lung nodule response, there was no significant difference in EFS or OS on the basis of 1q gain status.

Comparison With NWTS-5

We compared survival with similar patients with isolated pulmonary metastases treated in NWTS-5. In NWTS-5, patients with lung nodules visible on CT scan and not chest x-ray (CXR) were treated according to physician choice such that some were treated as stage IV and others were treated according to the local stage.[12] For the present analysis, we considered only patients treated as stage IV. The local stage distribution of patients was similar between NWTS-5 and AREN0533 (Table A1). The median age was higher in NWTS-5 (55 months) compared with AREN0533 (50 months), and there was a preponderance of females in NWTS-5 (63.4%) compared with AREN0533 (51.5%). Four-year EFS estimates for NWTS-5 and AREN0533 were 72.5% (95% CI, 66.9% to 78.1%) and 85.4% (95% CI, 80.5% to 90.2%; $P < .001$; Fig 5A), respectively. Four-year OS estimates for NWTS-5 and AREN0533 were 84.0% (95% CI, 79.4% to 88.6%) and 95.6% (95% CI, 92.8% to 98.4%; $P < .001$; Fig 5B), respectively. To assess whether the improved survival in AREN0533 was explained solely by greater inclusion of patients with small nodules, we repeated the comparison excluding patients in AREN0533 with lung nodules < 10 mm. In this comparison, 4-year EFS for NWTS-5 and AREN0533 were 72.48% (95% CI, 66.0% to 78.1%) and 82.5% (95% CI, 75.1% to 89.9%; $P = .032$), respectively. Four-year OS

Table 1. Outcomes According to 1q Gain Status

Group	No. (%)	4-year EFS, % (95% CI)	*P*	4-year OS, % (95% CI)	*P*
Incomplete lung nodule response					
1q gain+	42 (36.2)	86 (72.2 to 99.3)	.15	93 (83.1 to 100)	.45
1q gain-	74 (63.8)	92 (84.4 to 99.8)		96 (90.4 to 100)	
Complete lung nodule response					
1q gain+	21 (21.9)	57 (73.4 to 100)	.001	89 (73.4 to 100)	.16
1q gain-	75 (78.1)	86 (73.4 to 100)		97 (73.4 to 100)	

Abbreviations: EFS, event-free survival; OS, overall survival.

estimates for NWTS-5 and AREN0533 were 84.0% (95% CI, 79.4% to 88.6%) and 92.9% (95% CI, 88% to 97.9%; $P = .007$), respectively.

Adverse Events and Toxicities

Twenty-two events in 12 patients were reported through the Adverse Event Expedited Reporting System, 14 receiving Regimen M and eight receiving DD4A (Table A2). Two patients died, one in the first 6 weeks due to surgical complications and one receiving Regimen M of undetermined cause. Three patients developed sinusoidal obstruction syndrome, one receiving DD4A (grade 3) and two receiving Regimen M (grade 2 and 3). The rate of grade 3 to 5 nonhematologic toxicities with Regimen M was low (Table A3).

DISCUSSION

The risk stratification and treatment strategies of AREN0533 resulted in survival estimates that were superior to those achieved in previous studies of patients with FHWT and isolated pulmonary metastases. The treatment approach avoided initial lung RT in approximately 40% of patients, which is a clinically significant advance because lung RT is a contributing factor to congestive heart failure, pulmonary fibrosis, and breast cancer in Wilms tumor survivors.[13-15] Patients with lung nodule CR achieved excellent OS without initial lung RT, although there was a trend toward more events than expected. Studies from SIOP also omitted lung RT in patients with lung nodule CR after 6 weeks of chemotherapy, although these studies differed from AREN0533 in several ways. Whereas AREN0533 required that pulmonary CR be achieved through chemotherapy, SIOP studies allowed lung RT to be omitted if CR was achieved by either chemotherapy or pulmonary metastasectomy. In SIOP 93-01, 67% of patients with isolated pulmonary metastases achieved CR after the first 6 weeks of chemotherapy (compared with 42% in AREN0533) and an additional 17% achieved CR after pulmonary metastasectomy. The chemotherapy in the first 6 weeks of SIOP 93-01 was more dose intensive (100 mg/m^2 doxorubicin and 135 μg/kg dactinomycin) compared with AREN0533 (45 mg/m^2 doxorubicin and 45 μg/kg dactinomycin), perhaps explaining the higher CR rate. In addition, imaging studies in the SIOP study were not centrally reviewed, and the definition of CR may have been more stringent in AREN0533. In SIOP 93-01, the 5-year EFS and OS estimates for nonanaplastic Wilms tumor were 77% and 87%, respectively, compared with 4-year EFS of 85% and 96% in AREN0533.[5] Although a greater percentage of patients were spared lung RT in SIOP 93-01, patients received a cumulative doxorubicin dose of 350 mg/m^2, compared with 150 mg/m^2 with DD4A and 195 mg/m^2 with Regimen M. Importantly, AREN0533 demonstrates that patients with lung

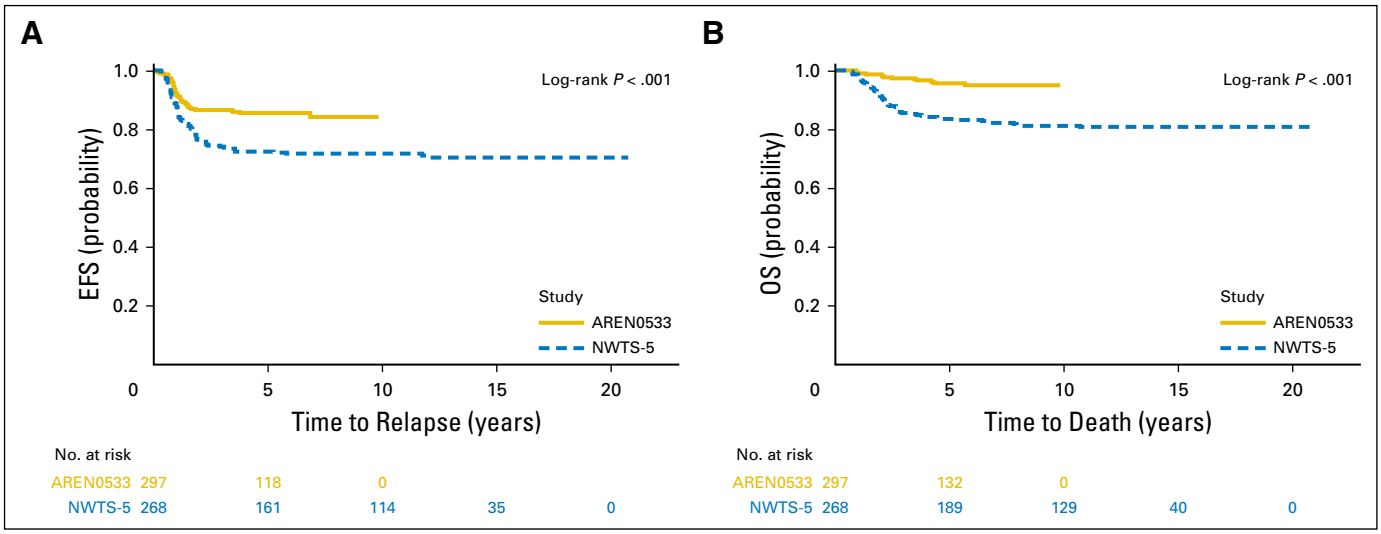

Fig 5. (A) Event-free survival (EFS) and (B) overall survival (OS) for patients with isolated pulmonary metastases in AREN0533 compared with NWTS-5.

nodule CR had outstanding OS without initial lung RT in the context of relatively low cumulative anthracycline exposure.

Patients who did not achieve a pulmonary CR at week 6 were treated with Regimen M and lung RT. With this approach, the 4-year EFS estimate approached 89%, which was significantly better than the null hypothesis of 75%. However, Regimen M has the potential for late effects, notably, an increased risk of secondary leukemia associated with cyclophosphamide and etoposide.[16,17] There is also a risk of infertility related to the use of cyclophosphamide, which had a cumulative dosage of 8.8 gm/m^2 on Regimen M, particularly in boys.[18] The significance of these risks should be balanced against the improvement in survival achieved.

Local stage distribution was markedly different between AREN0533 and the SIOP studies because of differences in the staging systems. Whereas 36% of patients with isolated pulmonary metastases in SIOP 93-01 had local stage III disease, 80% of patients in AREN0533 had local stage III. The difference is explained by the practice in the NWTS/COG staging system to consider patients who receive chemotherapy before nephrectomy to have local stage III (37% of patients in AREN0533). The consequence is that more patients received flank/abdominal RT in AREN0533 compared with the SIOP studies. The practice of giving abdominal RT to all patients who receive preoperative chemotherapy is under discussion by the COG Renal Tumor Committee.

Historically, patients with Wilms tumor were considered to have pulmonary metastases if lung nodules were visible on CXR. The introduction of CT scans posed the dilemma of how to treat patients with lung nodules visible on CT but not CXR, so-called CT-only nodules. Approximately 17% to 26% of such nodules were proven benign by biopsy in previous studies.[19,20] Moreover, inter-reader variability has been documented among radiologists in the detection of lung nodules.[21,22] Despite the imperfect specificity of chest CT scan for identifying malignancy, several cooperative group studies found that the presence of CT-only lung nodules was associated with inferior outcome.[23,24] Analysis of patients with CT-only nodules enrolled in NWTS-4 and -5 showed that 5-year EFS was greater for patients receiving doxorubicin than for those receiving only vincristine/dactinomycin (80% *v* 56%; $P = .004$). There was no difference in EFS according to whether lung RT was given.[12] These findings led to the design of AREN0533, where all patients with lung nodules received doxorubicin but lung RT was omitted for patients with CR.

The AREN0533 study was the first to incorporate a consistent definition of metastatic disease and allowed for observation of lung nodules over time. Among 292 patients whose lung nodules were evaluable for response, only 12 (4%) had SD during the first 6 weeks of chemotherapy, suggesting a low prevalence of static entities such as granulomas. Biopsy remains the gold standard to define histology and was strongly encouraged; however, only 23 of 175 patients (13.1%) with incomplete radiologic lung nodule response underwent biopsy, 16 of whom did not have viable tumor. This result should not be generalized because there was likely selection bias underlying which patients underwent biopsy. However, these data will be presented in future COG studies to more strongly encourage biopsy of residual nodules.

The patients in AREN0533 with LOH at 1p and 16q had 100% EFS and OS when treated with Regimen M and lung RT. This represents a marked improvement compared with NWTS-5.[2] A post hoc analysis of the prognostic value of 1q gain using the AREN0533 treatment paradigm showed that among patients with incomplete lung nodule response, there was no significant difference in EFS or OS according to 1q gain status, suggesting that Regimen M overcame the negative prognostic effect of 1q gain. By contrast, in patients with lung nodule CR, EFS was markedly inferior in patients with 1q gain. This important observation indicates that the presence of 1q gain provides a valuable method to identify patients with lung nodule CR who are not good candidates for omission of lung RT.

In summary, patients with isolated lung metastases and lung nodule CR after 6 weeks of therapy had excellent OS when treated initially without lung RT in the setting of low cumulative doxorubicin exposure. Patients with lung nodule IR or LOH 1p/16q had improved EFS and excellent OS using Regimen M and lung RT. These results provide a benchmark for future studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: David B. Dix, Nita L. Seibel, Geetika Khanna, James R. Anderson, Elizabeth A. Mullen, James I. Geller, John A. Kalapurakal, Peter F. Ehrlich, Marcio Malogolowkin, Paul E. Grundy, Conrad V. Fernandez, Jeffrey S. Dome
Collection and assembly of data: David B. Dix, Yueh-Yun Chi, Geetika Khanna, Eric Gratias, James R. Anderson, Elizabeth A. Mullen, James I . Geller, John A. Kalapurakal, Arnold C. Paulino, Elizabeth J. Perlman, Peter F. Ehrlich, Marcio Malogolowkin, Julie M. Gastier-Foster, Elizabeth Wagner, Paul E. Grundy, Jeffrey S. Dome
Data analysis and interpretation: David B. Dix, Yueh-Yun Chi, Geetika Khanna, Eric Gratias, James R. Anderson, Elizabeth A. Mullen, James I . Geller, John A. Kalapuraka, Arnold C. Paulino, Elizabeth J. Perlman, Peter F. Ehrlich, Marcio Malogolowkin, Julie M. Gastier-Foster, Paul E. Grundy, Conrad V. Fernandez, Jeffrey S. Dome
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Affiliations

David B. Dix, British Columbia Children's Hospital, Vancouver, British Columbia; **Paul E. Grundy**, University of Alberta, Edmonton, Alberta; **Conrad V. Fernandez**, Dalhousie University, Halifax, Nova Scotia, Canada; **Nita L. Seibel**, National Cancer Institute, Bethesda, MD; **Yueh-Yun Chi**, University of Florida, Gainesville, FL; **Geetika Khanna**, Washington University School of Medicine, St Louis, MO; **Eric Gratias**, University of Tennessee College of Medicine Chattanooga, Chattanooga, TN; **James R. Anderson**, Merck Research Laboratories, North Wales, PA; **Elizabeth A. Mullen**, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA; **James I. Geller**, Cincinnati Children's Hospital Medical Center, Cincinnati; **Julie M. Gastier-Foster** and **Elizabeth Wagner**, Nationwide Children's Hospital; **Julie M. Gastier-Foster**, The Ohio State University College of Medicine, Columbus, OH; **John A. Kalapurakal**, Lurie Comprehensive Cancer Centre of Northwestern University; **Elizabeth J. Perlman**, Ann and Robert H. Lurie Children's Hospital, Chicago, IL; **Arnold C. Paulino**, MD Anderson Cancer Center, Houston, TX; **Peter F. Ehrlich**, University of Michigan, Ann Arbor, MI; **Marcio Malogolowkin**, University of California at Davis Comprehensive Cancer Center, Sacramento, CA; **Jeffrey S. Dome**, George Washington University School of Medicine and Health Sciences, Washington, DC; on behalf of the AREN0533 Study Committee.

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David B. Dix
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Nita L. Seibel
No relationship to disclose

Yueh-Yun Chi
No relationship to disclose

Geetika Khanna
No relationship to disclose

Eric Gratias
Employment: eviCore Healthcare
Stock or Other Ownership: eviCore Healthcare

James R. Anderson
Employment: Merck

Elizabeth A. Mullen
No relationship to disclose

James I. Geller
No relationship to disclose

John A. Kalapurakal
No relationship to disclose

Arnold C. Paulino
Employment: MD Anderson Cancer Center
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No relationship to disclose

Peter F. Ehrlich
No relationship to disclose

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No relationship to disclose

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Paul E. Grundy
No relationship to disclose

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Appendix

Table A1. Demographics of Patients With Stage IV FHWT With Lung as the Only Metastatic Site

Characteristic	AREN0533 No.	AREN0533 %	NWTS-5 No.	NWTS-5 %	*P*
Gender					
Male	153	48.5	98	36.6	.003
Female	144	51.5	170	63.4	
Median age, months (range)	50 (6.8-350.4)		55 (9-211.1)		.024
Local stage					
I	10	3.4	6	2.2	
II	50	16.8	63	23.5	.11
III	237	79.8	199	74.3	
Race					
White	210	70.8			
Black/African American	45	15.3	*		
Others	6	2.1			
Unknown	36	11.8			
Ethnicity					
Hispanic or Latino	35	13.4			
Not Hispanic or Latino	245	81.1	*		
Unknown	17	5.5			

Abbreviation: FHWT, favorable histology Wilms tumor.
*Race and ethnicity were reported as a combined category in NWTS-5.

Table A2. Reportable Adverse Events in Patients With Isolated Pulmonary Metastases in AREN0533

Regimen	Event	Grade
DD4A	Death due to postoperative complications	5
DD4A	CPK increased	4
DD4A	Cardiac troponin I increased	3
DD4A	Ileus	4
DD4A	Infections and infestations—other, specify infection with grade 3 or 4 neutrophils (ANC $<$ 1.0 $\times$ 10e9/L): abdomen NOS	4
DD4A	Tumor lysis syndrome	4
DD4A	Urinary tract obstruction	4
DD4A	Hepatobiliary disorders—other, specify SOS	3
M	Infections and infestations—other, specify infection with grade 3 or 4 neutrophils (ANC $<$ 1.0 $\times$ 10e9/L): lung (pneumonia)	4
M	Pneumonitis	4
M	Adult respiratory distress syndrome	4
M	Bronchopulmonary hemorrhage	4
M	Hepatobiliary disorders—other, specify SOS	2
M	Pericardial effusion	4
M	Platelet count decreased	4
M	White blood cell decreased	4
M	Pulmonary hypertension	4
M	Small intestinal obstruction	4
M	Bone marrow hypocellularity	3
M	Sepsis	4
M	Death NOS	5
M	Hepatobiliary disorders—other, specify SOS	3

NOTE. Grade 5 toxicities, grade 4 unexpected at least possibly related to therapy, and all grades of SOS were considered reportable.
Abbreviations: ANC, absolute neutrophil count; CPK, creatinine phosphokinase; DD4A, vincristine/dactinomycin/doxorubicin; M, four cycles of cyclophosphamide/etoposide in addition to DD4A drugs; NOS, not otherwise specified; SOS, sinusoidal obstruction syndrome.

Table A3. Grade 3/4/5 Nonhematologic Toxicities Associated With Regimen M

Primary Category	Adverse Event	Regimen M (n = 149)	
		No.	%
Cardiac disorders	Pericardial effusion	1	0.7
Gastrointestinal disorders	Colitis	2	1.3
	Diarrhea	2	1.3
	Enterocolitis	1	0.7
	Ileus	2	1.3
	Mucositis oral	5	3.4
	Nausea	5	3.4
	Small intestinal obstruction	4	2.7
	Typhlitis	2	1.3
	Vomiting	3	2.0
General disorders and administration site conditions	Fatigue	1	0.7
	Fever	4	2.7
	Infusion-related reaction	1	0.7
Hepatobiliary disorders	Hepatobiliary disorders—other, specify	2	1.3
Immune system disorders	Anaphylaxis	1	0.7
Infections and infestations	Catheter-related infection	1	0.7
	Enterocolitis, infectious	4	2.7
	Infections and infestations—other, specify	21	14.1
	Lung infection	3	2.0
	Mucosal infection	1	0.7
	Otitis media	2	1.3
	Sepsis	4	2.7
	Skin infection	1	0.7
	Stoma site infection	1	0.7
	Upper respiratory infection	4	2.7
	Urinary tract infection	2	1.3
Investigations	ALT increased	1	0.7
	AST increased	1	0.7
	Creatinine increased	1	0.7
	GGT increased	1	0.7
	Weight loss	3	2.0
Metabolism and nutrition disorders	Anorexia	2	1.3
	Dehydration	5	3.4
	Hyperglycemia	2	1.3
	Hypocalcemia	2	1.3
	Hypokalemia	8	5.4
	Hyponatremia	4	2.7
	Hypophosphatemia	2	1.3
Musculoskeletal and connective tissue disorders	Chest wall pain	1	0.7
	Generalized muscle weakness	1	0.7
	Muscle weakness lower limb	1	0.7
	Muscle weakness upper limb	1	0.7
Nervous system disorders	Peripheral motor neuropathy	3	2.0
	Peripheral sensory neuropathy	1	0.7
	Seizure	2	1.3
	Syncope	1	0.7
Renal and urinary disorders	Acute kidney injury	1	0.7
	Hematuria	1	0.7
	Urinary tract obstruction	2	1.3
	Urinary tract pain	1	0.7
Respiratory, thoracic, and mediastinal disorders	Adult respiratory distress syndrome	1	0.7
	Dyspnea	1	0.7
	Hypoxia	1	0.7
	Respiratory failure	1	0.7
Skin and subcutaneous tissue disorders	Pruritus	1	0.7
Vascular disorders	Hypertension	3	2.0
	Hypotension	3	2.0
	Vascular disorders—other, specify	2	1.3

Abbreviations: GGT, γ-glutamyltransferase; Regimen M, four cycles of cyclophosphamide/etoposide in addition to vincristine/dactinomycin/doxorubicin.